Efficacy of Intraperitoneal Bupivacaine on Postoperative Analgesia in Laparoscopic Cholecystectomy: A Meta-analysis

Linnelle Stacy T. Lao, MD; Pierre Pepito R. Hao, MD and Maila Rose L. Torillo, MD, FPCS, FPSGS

Department of Surgery, Chinese General Hospital and Medical Center

The analgesic effect of intraperitoneal bupivacaine has been widely studied, but with controversial results.

Objective: To determine the efficacy of intraperitoneal bupivacaine on producing postoperative analgesia in patients who underwent laparoscopic cholecystectomy.

Methods: A systematic literature search on the use of intraperitoneal bupivacaine in reducing postoperative pain was done using Medline and Cochrane. The search yielded 6 randomized controlled trials, involving a total of 440 patients. Mean differences in visual analog pain score at 0, 2, 4, 6, 8, 12, and 24 hours post-surgery were pooled using random effects model.

Results: Overall, there was a significant reduction of pain score in the bupivacaine group with VAS score of -0.55 cm (95% CI, -0.80 to -0.31). Subgroup analysis at 0, 2, 4, 6, 8, and 12 hours post-surgery showed statistically significant mean differences in the VAS score of -1.59 cm (95% CI, -2.31 to -0.86), -0.60 cm (95% CI, -1.02 to -0.17), -0.80 cm (95% CI, -1.34 to -0.26), -0.85 cm (95% CI, -1.46 to -0.24), -0.64 cm (95% CI, -1.12 to -0.16), and -0.38 cm (95% CI, -0.68 to -0.08), respectively, in favor of the bupivacaine group. However, at 24 hours post-surgery, there was no statistically significant mean difference in the VAS score of -0.09 cm (95% CI, -0.49 to 0.31).

Conclusion: Intraperitoneal bupivacaine instillation among patients undergoing laparoscopic cholecystectomy is effective in providing postoperative analgesia specifically in the first 12 hours post-op.

Key words: intraperitoneal bupivacaine, bupivacaine, laparoscopic cholecystectomy, postoperative pain, pain

Laparoscopic cholecystectomy is well known as the gold standard in the treatment of benign symptomatic gallbladder pathologies.[1] Aside from its minimally invasive approach, its advantages over open cholecystectomy are reflected consistently on multiple randomized clinical trials. These include shorter postoperative hospital stay, shorter convalescence period, better cosmesis, and improved pulmonary function compared to open surgical approach.[1,2,3] However, one noted morbidity associated with abdominal laparoscopic procedure is the presence of considerable reports of postoperative pain.[3,4] As a result, the advantage of laparoscopy over conventional approach on this specific outcome is viewed with conflicting results among different clinical trials.[4]

Multiple mechanisms are involved in the generation of nociception in patients who underwent laparoscopic cholecystectomy. These include the following causations: traumatic destruction of somatic free nerve endings secondary to abdominal incision, parietal peritoneal distention, disruption of visceral nerve endings in the gallbladder bed, release of endogenous inflammatory cytokines, phrenic nerve irritation, irritation of peritoneum from blood, bile spillage, or by carbon dioxide, and somatoform or psychogenic causes.[2,4,5,12] Various analgesic managements were done with variable reported success rates. These include the following: intravenous administration of acetaminophen, selective COX inhibitors, opioids, local instillation of anesthetic agents (e.g. lidocaine, bupivacaine), intraperitoneal or intravenous administration of steroids, optimization of fluid and electrolyte imbalances, and comprehensive patient support services.[2,4,5,6] Multiple reviews have demonstrated the heterogeneity of clinical trials and have concluded that laparoscopic pain is multifactorial in nature. Although, various methods of analgesia produced

significant short term advantages, it does not usually translate into shorter hospital stay and less consumption of analgesics.

Majority of clinical trials focus on whether local administration of anesthetics in the operative gallbladder site and in right subdiaphragmatic space will lead to significant outcomes in postoperative analgesia. Several studies showed that intraperitoneal instillation of bupivacaine resulted in a significant postoperative pain reduction, decrease in usage of supplementary analgesics, and shorter convalescence period.[3,5,6,7] In contrast, other trials noted short term benefits, but did not equate into significant terms.[12,17] Furthermore, combined intraperitoneal administration of lidocaine and COXibs showed significant postoperative pain relief as compared to systemic administration of COXibs and local lidocaine instillation.[5,6,7] The major advantage of local instillation maybe related to its direct nociceptic inhibition of free nerve endings injured in the gallbladder bed, its gradual peritoneal absorption into the systemic circulation, and the lack of systemic toxicities associated with direct systemic administration of NSAIDs.[1,3,6,7]

The objective of this study was to determine the efficacy of intraperitoneal administration of bupivacaine on producing post-operative analgesia among the post-laparoscopic cholecystectomy population.

Methods

The lists of published articles were obtained using Medline and Cochrane databases from inception of the database until September 2015. The search conducted used the following MeSH terms: laparoscopic cholecystectomy AND [intraperitoneal bupivacaine OR bupivacaine] AND [post-operative pain OR pain] AND randomized controlled trial. Additional articles were obtained from the reference lists of the selected published articles. Search was limited to English language only.

All articles included in this study met the following inclusion criteria: 1) the study was a randomized controlled trial, 2) intraperitoneal bupivacaine was compared with placebo alone, and 3) participants underwent elective laparoscopic cholecystectomy. Exclusion criteria included: 1) intraperitoneal bupivacaine combined with other interventions, 2) included participants had acute cholecystitis or gallstone pancreatitis prior to surgery, 3) laparoscopic cholecystectomy converted to open surgery, 4) common bile duct exploration, and 5) non-human trials.

Obtained articles were reviewed by 3 researchers separately, and a consensus was reached with regards to the outcome measurements of this study. The primary outcome measured in this study was the pain score at 0, 2, 4, 6, 8, 12, and 24 hours after surgery. Pain scores were measured using a 10-cm visual analog scale (VAS), which was labeled "no pain" at 0 cm and "worst possible pain" at 10 cm. The mean and standard deviations were taken from the tables, and estimated from the graphs included in the article. In studies without specified mean or standard deviations, values were computed using the 25th and 75th percentile rank. Computation of the mean difference between the bupivacaine group and control group was done using the Review Manager 5.3 software. Mean difference with a negative value favors the bupivacaine group over the control group.

Secondary outcomes included analgesic requirements of patients undergoing laparoscopic surgery measured as to the amount of analgesic consumed, frequency of analgesic requirements, and number of participants requiring additional analgesia. Other outcome measures included were the respiratory function of the participants, the postoperative symptoms, participant's recovery index as measured by the time to start oral intake and to start ambulation, and the length of hospital stay.

Results

Preliminary literature search identified 127 articles for the meta-analysis. Abstracts of each article were reviewed, and 117 articles did not meet the inclusion criteria. Four articles were excluded due to incomplete data for statistical analysis.[10-13] (Figure 1)

This meta-analysis included six articles, involving a total of 440 participants.[14-19] Risks of bias were analyzed to ensure the quality of each article as shown in Table 1. Details of each article are summarized in Table 2. After induction of 10-14 mmHg of pneumoperitoneum, Szem et. al, and Mraovic et. al. instilled the 100mg in
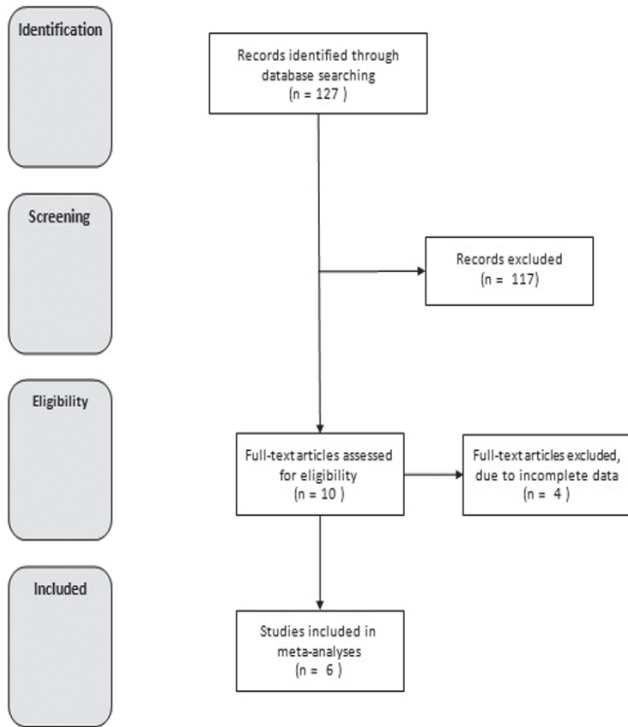
Figure 1. Flow chart of article selection

100mL and 75mg in 15mL bupivacaine solution, respectively, into the subdiaphragmatic space, Glisson's capsule, and the subhepatic space including the gallbladder using the epigastric trochar under direct visualization.[14,16] After removal of the gallbladder from the intra-abdominal cavity, Mraovic, et al. instilled another 75mg in 15 mL bupivacaine solution onto the gallbladder bed,[16] while Castillo-Garza, et al., Ahmad, et al., and Nupur, et al. instilled 100 mg in 20 mL bupivacaine solution onto the gallbladder bed.[15,18,19] Ahmad, et al. also placed a 3x3 inch surgicel soaked in the bupivacaine solution onto the gallbladder bed prior to closing.[19] Almost all of the trials included instilled a fixed amount of bupivacaine.[14-16,18,19] However, the study by Elfberg, et al. based the quantity of instilled bupivacaine on the participant's body weight (2mg/kg), but the volume and strength of bupivacaine were not indicated for each participant.[17] Five trials had an overall significant improvement in the postoperative pain during the first 24 hours.[14-16,18,19]

Four trials analyzed the analgesic requirements of the participants after surgery using three different parameters - amount of analgesic consumed, frequency of analgesic requirements, and number of participants requiring additional analgesia.[14,15,16,18] Two trials showed

Table 1. Risk of bias of included articles.

	Szem 1996	Mraovic 1997	Elfberg 2000	Castillo-Garza 2012	Nupur 2014	Ahmad 2015
Random sequence generation (selection bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment (selection bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of participants and personnel (performance bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of outcome assessment (detection bias)	Low risk	Low risk	Low risk	Unclear risk	Low risk	High risk
Incomplete outcome data (attrition bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selective reporting (reporting bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

[a]Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Table 2. Summary of included studies.

Study and year	Patients (B/C)	Volume of B used (mL)	Strength of B(%)	Total quantity of B (mg)	Location of instillation	Timing of instillation in relation to GB dissection	Time intervals of VAS (hr)	Sig difference
Szem 1996	26/29	100	0.1	100	SHS, SDS	Before	6,12,18,24	YES
Mraovic 1997	40/40	30	0.5	75	GBB, SHS, SDS	Before, After	0.5, 4, 8, 12, 24	YES
Elfberg 2000	33/32	ns	ns	137	GBB	After	2, 4, 8, 24, 48	NO
Castillo-Garza 2012	30/30	20	0.5	100	GBB	After	0, 6, 12, 24	YES
Nupur 2014	30/30	20	0.5	100	GBB	After	0, 1, 2, 4, 6, 8, 12, 24	YES
Ahmad 2015	60/60	20	0.5	100	GBB	After	4, 12, 24	YES

Legend: B- bupivacaine; C- control; ns- not stated; GBB - gallbladder bed; SHS - subhepatic space; SDS - subdiaphragmatic space; GB - gallbladder; VAS - visual analog scale; Sig - significant

no statistical difference in the amount of analgesic consumed and the frequency of analgesic requirement between the two groups at different postoperative periods.[14,18] Another trial showed no statistically significant difference in the amount of analgesia consumed between the bupivacaine and control group in participants with VAS <5cm. However, there was a significantly less amount of analgesic used in those participants with a VAS>5cm.[16] One trial showed a statistically significant decrease in the number of patients requiring analgesia in the bupivacaine group compared with control.[15]

One trial reported on the respiratory function with the use of peak expiratory flow before and after laparoscopic cholecystectomy. It showed no significant differences between the two groups at any time after surgery.[17]

Postoperative symptoms were reported in three trials, showing no significant differences between the two groups. Postoperative symptoms include nausea, vomiting, fever,[15] shoulder pain,[14] bradycardia, hypotension, urinary retention, pruritus, and headache.[19] Two trials reported on the participant's recovery index (time to start oral intake and time to start ambulation) with conflicting results. One reported that intraperitoneal bupivacaine significantly decreases the time to start oral intake by -1.43 hours (95%CI, -2.09 to -0.77) and ambulation by -1.01 hours (95%CI, -1.65 to -0.37),[19] while another reported no significant difference between the two groups- -1 hour (95%CI, -2.20 to 0.20) and -0.50 hour (95%CI, -2.30 to 1.30), respectively .[15] Quantitative analysis between the two studies showed a statistically significant difference between the two groups in favor of the bupivacaine group- -1.33 hours (95% CI, -1.91 to -0.75) for the time to start oral intake, and -0.95 hours (95% CI, -1.55 to -0.35) for the time to start ambulation (Figures 2 & 3).

Two trials investigated the effect of intraperitoneal bupivacaine on the length of hospital stay, but with conflicting results. One trial showed no significant difference in the length of hospital stay by -0.10 days (95%CI, -0.33 to 0.13) between the two groups[14], while the other one showed a significant decrease in the length of hospital stay by -0.30 days (95%CI, -0.52 to -0.08) in the bupivacaine group compared with the control.[19] Quantitative analysis between the two studies showed a statistically significant difference of -0.21 days (95% CI, -0.36 to -0.05) between the two groups in favor of bupivacaine group (Figure 4).
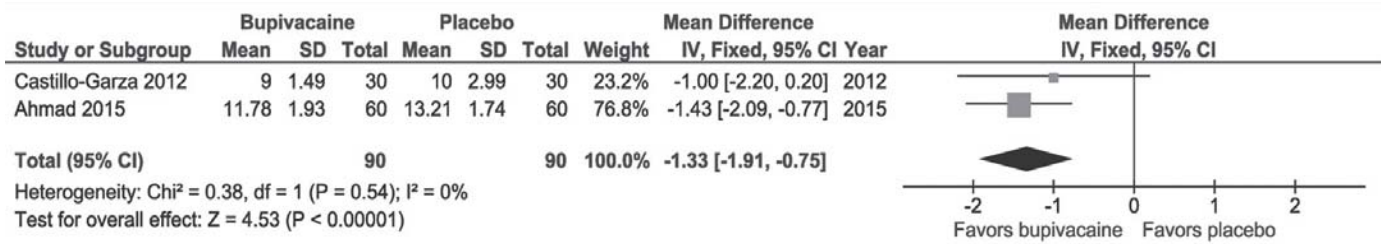
Figure 2. Forest plot illustrating the effect of bupivacaine versus placebo on the time to start oral intake.
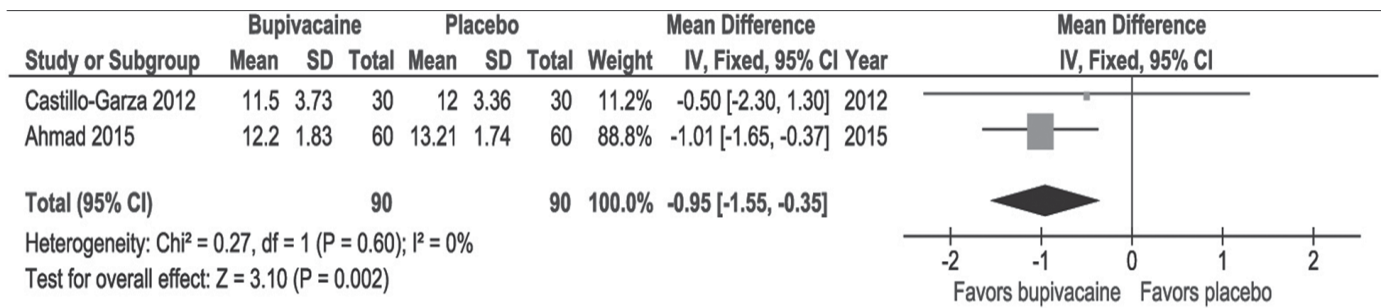

Figure 3. Forest plot illustrating the effect of bupivacaine versus placebo on the time to start ambulation.
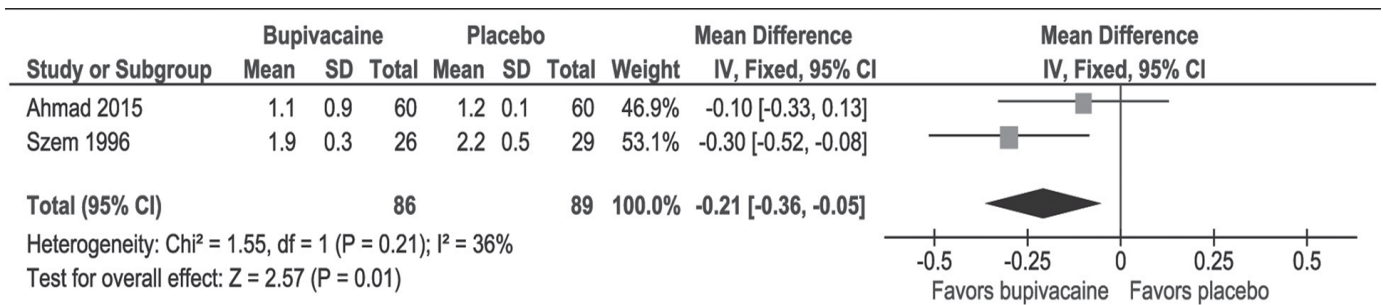

Figure 4. Forest plot illustrating the effect of bupivacaine versus placebo on the length of hospital stay.

There were sufficient data extracted from the six selected trials for quantitative analysis comparing the VAS scores of the participants in the two groups.[14-19] There were a total of 219 participants in the bupivacaine group, and 221 participants in the control group. Overall, there was a statistically significant mean difference in the VAS score of -0.55 cm (95% CI, -0.80 to -0.31) in favor of the bupivacaine group. There is a significant heterogeneity among the studies, having I^2 of 62.4% (Figure 5).

Subgroup analysis of different hour intervals between the two groups was done at 0, 2, 4, 6, 8, 12, and 24 hours post-surgery. In the initial postoperative period (0 hour), Castillo-Garza, et al. and Nupur, et al. individually showed a statistically significant difference of -1.50 cm (95% CI, -2.60 to -0.40)[15] and -1.65 cm (95% CI, -2.61 to -0.69),[18] respectively, in favor of the bupivacaine group. Analysis for the two studies showed that there were statistically significant mean differences in the VAS score of -1.59 cm (95% CI, -2.31 to -0.86),
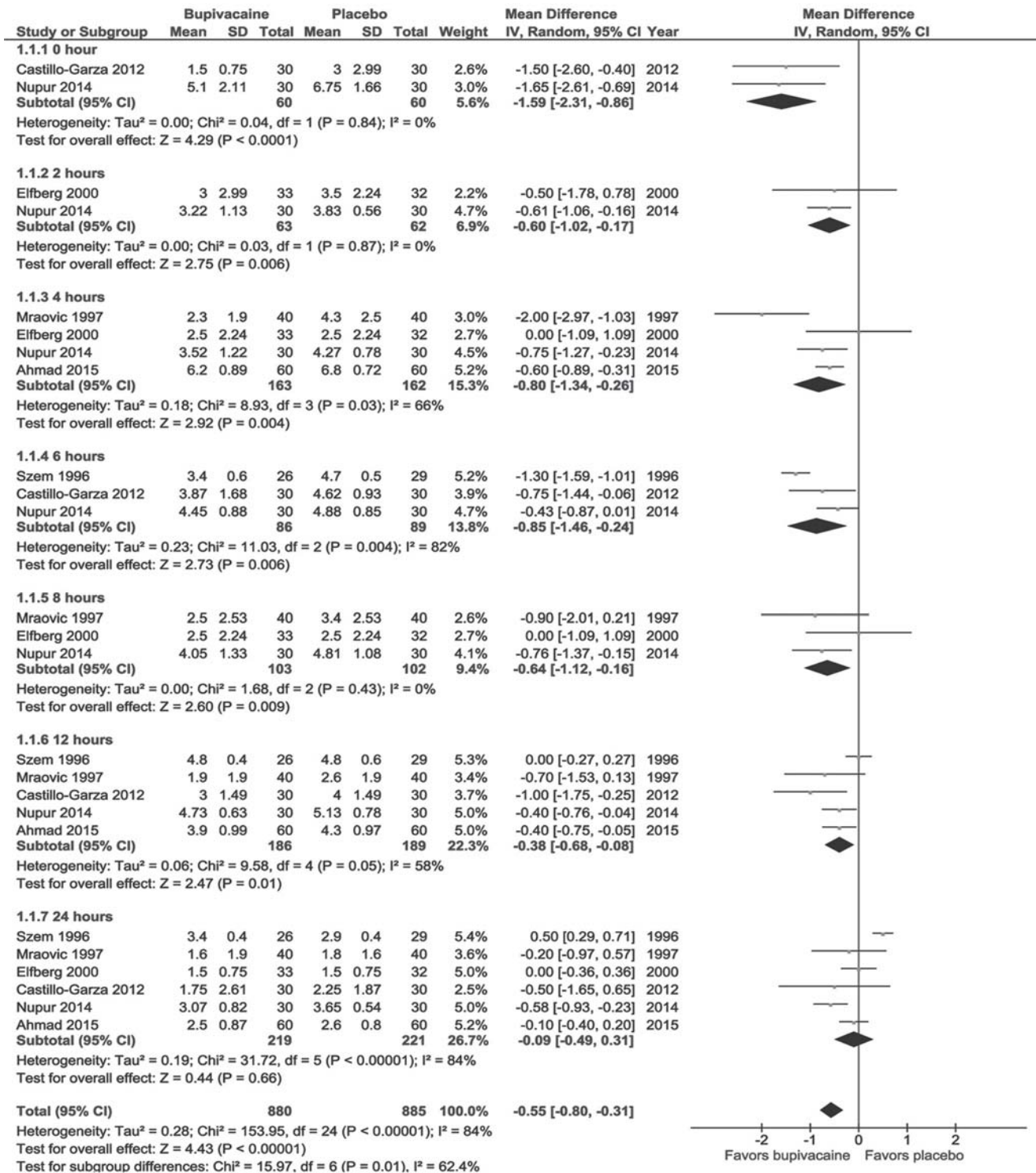
Figure 5. Forest plot illustrating the effect of bupivacaine versus placebo in visual analog scale (VAS) scores.

favoring bupivacaine group. At the second postoperative hour, Elfberg, et al. showed no significant difference of -0.50 cm (95%CI, -1.78 to 0.78);[17] while Nupur, et al. showed a significant difference of -0.61 cm (95%CI, -1.06 to -0.16) in favor of the bupivacaine group.[18] Overall, there was a statistically significant difference of -0.60 cm (95% CI, -1.02 to -0.17), in favor of the bupivacaine group at two hours after surgery. At the fourth postoperative hour, studies by Mraovic, et al., Nupur, et al. and Ahmad, et al. showed statistically significant difference of -2.00 cm (95% CI, -2.97 to -1.03),16 -0.75 cm (95%CI, -1.27 to -0.23),[18] and -0.60 cm (95%CI, -0.89 to -0.31),[19] respectively, in favor of the bupivacaine group. Contrarily, Elfberg, et al. showed no statistical difference of 0 cm (95%CI, -1.09 to 1.09) between the two groups.[17] Overall, there was a statistically significant difference of -0.80 cm (95% CI, -1.34 to -0.26), in favor of the bupivacaine group at four hours after surgery. At the sixth postoperative hour, Szem, et al. and Castillo-Garza, et al. showed statistically significant difference of -1.30 cm (95%CI, -1.59 to -1.01)[14] and -0.75 cm (95%CI, -1.44 to -0.06),[15] respectively, in favor of the bupivacaine group; while Nupur, et al. showed no statistically significant difference of -0.43 cm (95%CI, -0.87 to 0.01).[18] Overall, there was a statistically significant difference of -0.85 cm (95%CI, -1.46 to -0.24), in favor of the bupivacaine group at six hours after surgery. At the eighth postoperative hour, Nupur, et al. showed a statistically significant difference of -0.76 cm (95%CI, -1.37 to -0.15), in favor of the bupivacaine group;[18] while Mraovic, et al. and Elfberg, et al. showed no statistically significant difference of -0.90 cm (95%CI -2.01 to 0.21)[16] and 0.00 (95%CI -1.09 to 1.09),[17] respectively. Overall, there was a statistically significant difference of -0.64 cm (95% CI, -1.12 to -0.16), in favor of the bupivacaine group at eight hours after surgery. At the twelfth postoperative hour, Castillo-Garza, et al., Nupur, et al., and Ahmad, et al. showed significant differences of -1.00 cm (95%CI, -1.75 to -0.25),[15] -0.40 cm (95%CI, -0.76 to -0.04),[18] and -0.40cm (95%CI, -0.75 to -0.05),[19] respectively in favor of bupivacaine group. There were no statistically significant differences seen in the study of Szem, et al. and Mraovic, et al., wherein the difference is 0.00 cm (95%CI, -0.27 to 0.27)[14] and -0.70 cm (95% -1.53 to 0.13),[16] respectfully.

Overall, there was a statistically significant difference of -0.38 cm (95% CI, -0.68 to -0.08), in favor of the bupivacaine group at twelve hours after surgery. However, at the twenty-fourth postoperative hour, only Nupur, et al. showed a statistically significant difference of -0.58 cm (95% CI, -0.93 to -0.23), in favor of bupivacaine.[18] Szem, et al. showed a statistically significant difference of 0.50 cm (95%CI, 0.29 to 0.71) in favor of the placebo group.[14] Mraovic, et al., Elfberg, et al., Castillo-Garza, et al., and Ahmad, et al., all showed no significant difference of -0.20 cm (95% CI, -0.97 to 0.57),[16] 0.00 cm (95%CI, -0.36 to 0.36),[17] 0.50 cm (95% CI, -1.65 to 0.65),[15] and -0.10 cm (95% CI, -0.40 to 0.20),[19] respectively. Overall, there was no statistically significant mean difference in the VAS score of -0.09 cm (95% CI, -0.49 to 0.31) 24 hours after surgery (Figure 4).

Discussion

Instillation of local anesthetics after laparoscopic cholecystectomy for postoperative pain has been studied in different prospective randomized trials, wherein each provided heterogeneous results. This meta-analysis collated the results of the six selected trials in order to determine if there is an overall significance in the said procedure for postoperative pain. Laparoscopic cholecystectomy compared with conventional open cholecystectomy has been known to provide less hospital stay, better cosmesis, less postoperative pain and early recovery.[5-8,14] The use of bupivacaine is favored among anesthetics because of its characteristic longer duration of action and high potency.[9,11,13] Bupivacaine instillation produces a peak blood levels within 15-30 minutes[14,21] and could last for an average of 3 to 10 hours.[15] Plasma concentration between 0.92 and 1.14 µg/mL is achieved after instillation of 100 to 150 mg of bupivacaine, which is below its toxic level of 3-5 µg/mL.[20,21] Intraperitoneal route of administration of local anesthetics exposes the peritoneum to the blockade of the visceral nociceptive conduction, with an additional mechanism of analgesia. Large peritoneal surface absorbs the anesthetics, which may be responsible for prolongation of analgesia.[20]

Based on the results, there was a collective significant reported reduction in the postoperative pain among participants, who underwent bupivacaine instillation compared with control group until 12 hours post-surgery. However, at 24 hours post-surgery, VAS scores showed no statistical significance on both groups. The limited half-life of bupivacaine can explain its consistent short term effect in the studies.[15]

Despite significant reduction on VAS scores in favor of the bupivacaine group, conflicting results among trials were noted in terms of reduction of postoperative analgesic requirement on both groups. The lack of consistencies in the results regarding the effect of bupivacaine in individual studies is a matter of speculation. Ahmed, et al. stated that the minimal effect of bupivacaine versus the placebo group might be due to the small sample size and the manner of bupivacaine instillation.[19] In this study, bupivacaine-soaked surgicel was placed on the gallbladder bed after dissection. The minimal effect on the pain scores could be attributed to the diluting effect of saline irrigation on the operative site prior to the application of the surgicel. Furthermore, the vessel thrombosis brought about by electrocoagulation on the gallbladder bed might interfere with the absorption of the anesthetic.[19]

In the study by Elfberg, et al., a variable amount of bupivacaine was instilled according to the participant's weight in kilograms. Only participants in the heavier subgroups experienced a significant pain relief two hours after surgery, leading to an overall lack of significance in the result.[17] It is proposed that higher bupivacaine dosage can provide better pain control owing to its greater diffusion along a greater surface area.[18]

The analgesic effect is also affected by the timing and site of bupivacaine instillation. Application of the anesthetic before gallbladder resection might promote better absorption[18] and greater central neural sensitization suppression.[17] This is in addition of having the peak effect advantage of the anesthetic during gallbladder dissection.[14] The sites of instillation whether on the gallbladder bed or the subdiaphragmatic space may affect the outcome because both have different visceral innervation and different pain pathways.

Other factors include the volume, pressure and temperature of pneumoperitoneum, the volume of residual carbon dioxide that might cause diaphragmatic irritation, spillage of bile and blood that might interfere with absorption, instillation in a trendelenberg position versus supine,[18] the type and amount of postoperative analgesics used, and the amount of gallbladder traction from the liver bed during dissection.[14]

One limitation consistent in all studies regarding the pain scores is the inter-individual variability of pain thresholds and perception.[14-19]

Based on the study, materials used are widely available in the local setting and the technique provided by the literature virtually has a negligible learning curve. Therefore, the applicability of the results is feasible.

Conclusion

Overall, the result of this meta-analysis provides a conclusive significant correlation between intraperitoneal bupivacaine instillation and the short-term postoperative pain. However, its significance is confounded by multiple factors, as discussed above. A randomized controlled trial is recommended using a larger sample size and controlling each confounding factors by using a standard dosage of bupivacaine and a uniform set of postoperative analgesics, and by doing subgroup analysis on the timing and site of instillation.

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